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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/346,069	07/01/1999	BRUCE A. KEYT	A-/62326-2/R	1979

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FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP
SUITE 3400 FOUR EMBARCADERO CENTER
SAN FRANCISCO, CA 941114187

EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	15

DATE MAILED: 03/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/346,069	Applicant(s) KEYT ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15 and 18-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 18-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed January 15, 2002 has been entered.

Response to Arguments

The rejection of claims under 35 USC, 112, second paragraph, are withdrawn in view of the amendment to the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claim 21 as amended is objected to because of the following informalities: "is modified" should be –are modified--. Appropriate correction is required.

Oath/Declaration

This application presents a claim for subject matter not originally claimed or embraced in the statement of the invention. The subject matter is amino acid modifications of Phe 17, Ile 46 and Ile 43 in VEGF as presented in US Application 08/691,794, to which the instant application is now claiming priority as a CIP. A supplemental oath or declaration is required under 37 CFR 1.67. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02.

Claim Rejections - 35 USC § 101

Claims 19-21, 23, 25, 27, 29-32 remain rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claimed nucleic acid reads on naturally occurring bovine VEGF, which is a variant of native human VEGF with the amino acid modifications required by the claims.

Applicants argue that a "VEGF variant of native VEGF" is required by the claims to have a least one amino acid of native VEGF modified, and modification by definition involves human manipulation of the VEGF sequence. The argument has been fully considered, but is not

persuasive. There are modifications by, for example, mutagenesis that occur in nature. There is no definition in the specification to restrict variants of VEGF to only those made by man and which no not occur in nature. Additionally, VEGF has been found in a variety of organisms including zebrafish (GenBank Accession No. AAC41274), quail (GenBank Accession No. CAA75799), *Xenopus laevis* (GenBank Accession No. AAB63680), pit viper (GenBank Accession No. AAK52103), and even an orf virus (GenBank Accession No. AAD03735). Therefore, even to say a variant of a mammalian VEGF would not exclude that variant being from a fish or other naturally occurring source.

If it is Applicants' intention that the modification is by the hand of man and does not encompass naturally occurring variants, then this rejection could be obviated by adding "non-naturally occurring" before "vascular endothelial cell growth factor (VEGF) variant of native VEGF" (lines 2-3 of claim 18).

Specification

The amendment filed January 15, 2002, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment to page 5, line 4, adding the paragraph with Phe 17, Ile 43 and/or Ile 46.

Applicant is required to cancel the new matter in the reply to this Office Action.

Double Patenting

Claim 18 remains rejected under the judicially created doctrine of double patenting over claim 1 of U. S. Patent No. 6,057,428 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent, for the reasons set forth in the previous Office action (paper #13, p. 2, line 33- p. 3, line 8).

Claim 15 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,057,428, for the reasons set forth in the previous Office action (paper #13, p. 3, lines 10-15).

Applicants' intention to postpone addressing the rejection until subject matter is indicated as allowable and in the even that claims are amended is acknowledged.

Claim Rejections - 35 USC § 112, First Paragraph

Claims 19-33 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous Office action (paper #13, p. 4, lines 5-20). There does not appear to be support in the instant specification for modification of the following amino acids as recited in the newly added claims: Phe 17, Ile 46 and Ile 43.

Applicants argue that the specification has been amended to include these modifications and provide written description. The argument has been fully considered, but is not persuasive. Applicants have also amended the priority of the instant application to claim benefit as a CIP of 08/691,794, which contains the above modifications. While priority may be amended, if the instant application did not originally (*i.e.*, as filed) incorporate the matter of 08/691,794 by reference, then added subject matter from 08/691,794 constitutes added new matter if it did not originally appear in the instant application or originally claimed priority application 08/567,200 and provisional 60/002,827.

Claims 18 and 15 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a VEGF variant which is the same as native VEGF except that it contains at least one amino acid modification in the KDR and/or FLT-1 region, wherein KDR is the binding domain of the KDR receptor and FLT-1 is the binding domain for the FLT-1 receptor, such that said amino acid modification results in modification of the binding affinity of said region(s) with respect to the binding affinity of the KDR and/or FLT-1 receptors to native VEGF, does not reasonably provide enablement for VEGF variants which differ in amino acid sequence from native VEGF in areas outside the KDR or FLT-1 region where those other modifications result in modification of the binding affinity of KDR and/or FLT-1. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims for the reasons set forth in the previous Office action (paper #13, beginning p. 4, line 21).

Applicants argue that the specification teaches that other modifications that do not affect the overall properties of the VEGF variant with respect to the KDR or FLT-1 regions (p. 16 of specification), and assays to evaluate the level of activity and binding to the VEGF variant are also disclosed, so that one skilled in the art could produce the claimed variant. The argument has been fully considered, but is not persuasive. The specification does not provide guidance to allow the skilled artisan to reasonably predict what other specific modifications would not affect the overall properties of the VEGF variant. What the claims does not require is that the change in binding affinity is due solely to a change(s) solely in the amino acid sequence of the KDR or FLT-1 region. Binding is a complex process, requiring binding not only to specific amino acids but also a necessary three-dimensional conformation so that the binding region(s) are in the required spatial orientation to allow contact with the receptor to which they bind. One would reasonably expect that mutations (amino acid substitutions, insertions or deletions, as allowed by the specification—see previous office action p. 5, lines 6-12) that significantly alter the three-dimensional structure of VEGF would affect its binding affinity to its receptors. However, which mutations would cause these changes and how binding affinity would be affected is not predictable. The specification provides no direction or guidance for predicting affects of mutations outside the KDR or FLT-1 regions. While different general types of mutations are disclosed (*e.g.*, insertions of 1-10 amino acids), and assays to test binding affinity are disclosed and were known in the art, it is maintained that because of broad claim language, the complex nature of the invention in terms of both structure and binding, the unpredictability of amino acid modification affect on binding affinity, the limited teachings and examples in the specification and the paucity of VEGF structural binding information in the prior art, it would require undue experimentation to practice the claimed

Applicants argue that not all VEGF variants with modified binding are being claimed, only those with modification in the specified binding regions, and it is not proper to exclude simple conserved modifications, for example, outside these binding regions or to require specifying which modifications do not alter binding to KDR or FLT-1, which would read

limitations into the claim which are not recited. The argument has been fully considered, but is not persuasive. The important point is that the claims do not require that the modifications to the binding regions are the modifications affecting the binding. While it seems reasonable to enable the VEGF variant to encompass modifications outside the binding regions which do not affect binding, the claims are not so limited.

Applicants argue that with the disclosed ability to screen by routine methods modified VEGF molecules enables the claims for their full breadth. The argument has been fully considered, but is not persuasive. As discussed above in the first paragraph for the response to this rejection, it is the undue experimentation required for the claims' full breadth that makes them not enabled.

Applicants argue that the same claim construction is consistent with that of US Patent '428 and '473. The argument has been fully considered, but is not persuasive. Each application is examined on its own merits.

Claim Rejections - 35 USC § 102

Claim 18 remains rejected under 35 U.S.C. 102(b) as being anticipated by Tischer et al. (US Patent 5,219,739, reference 11 cited by Applicants) for the reasons of record as set forth in the previous Office action on p. 6).

Applicants argue that as discussed for the rejection under 35 USC 101, "modification" denotes active manipulation by man to product the chance and neither VEGF of Tischer has such a modification and so the reference cannot anticipate the claim. The argument has been fully considered, but is not persuasive. As address in the arguments to the 101 rejection above, the examiner maintains that "modification" does not require human intervention. The bovine VEGF is modified relative to the human VEGF as disclosed by Tischer. Therefore, the limitations of the claim are met.

Claim Rejections - 35 USC § 103

Claim 15 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Tischer et al. (US Patent 5,219,739) for the reasons of record as set forth in the previous Office action beginning on p. 6).

Applicants argue that Tischer et al. does not teach of suggest the claimed composition with the modification. The argument has been fully considered, but is not persuasive. For the reasons above addressing the rejection under 35 USC 102 it does.

Note that the suggestion for amending the claims to overcome the rejection under 35 USC 101 would also obviate the above art rejections.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the

applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
March 13, 2002

LORRAINE SPECTOR
PRIMARY EXAMINER